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- (b) a substitution of a non-conservative replacement amino acid for the corresponding first vertebrate growth hormone residue where
- (i) a second vertebrate growth hormone exists for which the corresponding amino acid is a non-conservative substitution for the corresponding first vertebrate growth hormone residue, and/or
- (ii) the binding affinity for the first vertebrate growth hormone's receptor of a single substitution mutant of the first vertebrate growth hormone, wherein said corresponding residue, which is not alanine, is replaced by alanine, is at least 10% of the binding affinity of the wild-type first vertebrate growth hormone,
- (c) a deletion of a residue which is not part of the alpha helices of said vertebrate growth hormone corresponding to helices 1(7-34), 2(75-87), 3(106-127) and 4(152-183) of porcine growth hormone, such deleted residue furthermore not being a conserved residue in the vertebrate GH family, and
- (d) a deletion of a residue found in said first vertebrate growth hormone but deleted in a second reference vertebrate growth hormone, said polypeptide having growth hormone receptor antagonist activity,
- with the proviso that said polypeptide does not correspond to human growth hormone with all of the following substitutions and no others: Y111V, L113I, K115E, D116Q, E118K, E119R, G120L, Q122E, T123G, G126L, R127I and E129S.

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29 (thrice amended). A non-naturally occurring DNA molecule which comprise a coding sequence which encodes a growth hormone receptor antagonist which is a polypeptide which comprises an amino acid sequence comprising residues corresponding to residues 96-133 of bovine growth hormone which sequence is at least 50% identical to the amino acid sequence of a first vertebrate growth hormone, and wherein the amino acid position corresponding to amino acid Gly 119 of bovine growth hormone is an amino acid other than glycine or alanine, said polypeptide having growth hormone receptor antagonist activity,
with the proviso that said polypeptide does not correspond to human growth hormone with all of the following substitutions and no others: Y111V, L113I, K115E, D116Q, E118K, E119R, G120L, Q122E, T123G, G126L, R127I and E129S.

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66 (amended). A non-naturally occurring DNA molecule comprising a coding sequence encoding a growth hormone receptor antagonist which is a polypeptide which comprises an amino acid sequence which

(A) is at least 50% identical with the sequence of a first reference vertebrate growth hormone, and

(B) differs therefrom solely in that

(I) the amino acid position corresponding to amino acid Gly119 of bovine growth hormone is an amino acid other than glycine or alanine, and

(II) any additional differences, if any, between said amino acid sequence and the amino acid sequence of said first vertebrate growth hormone, are independently selected from the group consisting of

(a) a substitution of a conservative replacement amino acid for the corresponding first reference vertebrate growth hormone residue,

(b) a substitution of a non-conservative replacement amino acid for the corresponding first reference vertebrate growth hormone residue where

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- (i) a second reference vertebrate growth hormone exists for which the corresponding amino acid is a non-conservative substitution for the corresponding first reference vertebrate growth hormone residue, and/or
- (ii) the binding affinity for the first reference vertebrate growth hormone's receptor of a single substitution mutant of the first reference vertebrate growth hormone, wherein said corresponding residue, which is not alanine, is replaced by alanine, is at least 10% of the binding affinity of the wild-type first reference vertebrate growth hormone,
- (c) a deletion of a residue which is not part of the alpha helices of said reference vertebrate growth hormone corresponding to helices 1(7-34), 2(75-87), 3(106-127) and 4(152-183) of porcine growth hormone, such deleted residue furthermore not being a conserved residue in the vertebrate GH family, and
- (d) a deletion of a residue found in said first reference vertebrate growth hormone but deleted in a second reference vertebrate growth hormone,

said polypeptide having growth hormone receptor antagonist activity,

with the proviso that said first and second reference vertebrate growth hormones are both mammalian growth hormones.

81 (amended). A non-naturally occurring DNA molecule comprising a coding sequence encoding a growth hormone receptor

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antagonist which is a mutant polypeptide comprising an amino acid sequence, said polypeptide being a mutant of a vertebrate growth hormone, the amino acid sequence of said mutant of a vertebrate growth hormone comprising a substitution of the glycine of said vertebrate growth hormone corresponding to Gly119 of bovine growth hormone, with an amino acid other than glycine or alanine, said polypeptide having growth hormone receptor antagonist activity,

with the proviso that said polypeptide does not correspond to human growth hormone with all of the following substitutions and no others: Y111V, L113I, K115E, D116Q, E118K, E119R, G120L, Q122E, T123G, G126L, R127I and E129S.

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88 (amended). A method of reducing growth hormone activity in a mammalian subject which comprises administering to the subject a DNA molecule according to claim 81, under conditions conducive to the integration of said DNA into the genome of one or more cells of said subject, said subject subsequently expressing a growth hormone activity-antagonizing and pharmaceutically acceptable amount of said polypeptide, said polypeptide having growth hormone antagonist activity in said subject,

said polypeptide having mammalian growth hormone receptor antagonist activity,

whereby the growth hormone activity in said subject is reduced.

89 (amended). The method of claim 88 wherein the mammal suffers from an excessive growth rate.

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107 (amended). A non-naturally occurring DNA molecule comprising a coding sequence encoding a vertebrate growth hormone variant comprising an amino acid substitution of an amino acid, other than glycine or alanine, for the amino acid of said vertebrate growth hormone at the position corresponding to the glycine at position 119 of bovine growth hormone, wherein the growth hormone variant has vertebrate growth hormone inhibitory activity, with the proviso that said polypeptide does not correspond to human growth hormone with all of the following

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SB substitutions and no others: Y111V, L113I, K115E, D116Q, E118K, E119R, G120L, Q122E, T123G, G126L, R127I and E129S.

108 (amended). The DNA molecule of claim 107 where said variant differs from the vertebrate growth hormone solely at said position corresponding to the glycine at position 119 of bovine growth hormone.

109 (amended). A non-naturally occurring DNA molecule comprising a coding sequence encoding a vertebrate growth hormone variant comprising lysine at the position corresponding to the glycine at position 119 of bovine growth hormone, wherein the growth hormone variant has vertebrate growth hormone inhibitory activity.

110 (amended). A non-naturally occurring DNA molecule comprising a coding sequence encoding a vertebrate growth hormone variant comprising arginine at the position corresponding to the glycine at position 119 of bovine growth hormone, wherein the growth hormone variant has vertebrate growth hormone inhibitory activity.

111 (amended). A non-naturally occurring DNA molecule comprising a coding sequence encoding a vertebrate growth hormone variant comprising proline at the position corresponding to the glycine at position 119 of bovine growth hormone, wherein the growth hormone variant has vertebrate growth hormone inhibitory activity.

112 (amended). A non-naturally occurring DNA molecule comprising a coding sequence encoding a vertebrate growth hormone variant comprising tryptophan at the position corresponding to the glycine at position 119 of bovine growth hormone, wherein the growth hormone variant has vertebrate growth hormone inhibitory activity.

987 Sub #2
Please add the following new claims:

--114 (new). A non-naturally occurring DNA molecule encoding a vertebrate growth hormone variant, said variant having an amino acid sequence comprising a substitution of any amino acid other than glycine or alanine at the glycine corresponding